



Sublingual immunotherapy: the U.S. experience

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Purpose of review

It is likely that approval of allergen preparations for sublingual immunotherapy (SLIT) will soon occur in the United States. This article reviews experience with SLIT in this country, concentrating on the large, multicenter trials that will provide the evidence of safety and efficacy necessary to obtain that approval.

Recent findings

Large multicenter trials have been conducted with both grass and short ragweed. In five single-season studies with sublingual grass tablets, usually starting 4 months prior to and continuing through the pollen season, the combined symptom medication score was improved 20–28% relative to placebo-treated individuals. Short ragweed tablets, initiated 4 months prior to and continued through the pollen season, reduced symptom/medication scores by 24–26%. Similar results have been reported with short ragweed aqueous extract administered sublingually. To date, there has been only one small study each with house dust mite and cat allergen extracts. All of these studies were conducted with a single allergen. One small study, comparing timothy alone to the same dose of timothy combined with nine other pollen extracts, raised still unanswered questions regarding the efficacy of SLIT with multiple allergen mixes.

Summary

SLIT is coming to the United States. There will be approved allergen preparations for which the appropriate dosing for efficacy and safety has been established. It would be inappropriate to use the evidence generated by these large studies to justify off-label use of allergen extracts approved for injection or the administration of multiple allergen preparations sublingually.

Keywords

immunotherapy, multiallergen immunotherapy, short ragweed, sublingual immunotherapy, timothy grass

INTRODUCTION

Sublingual immunotherapy (SLIT) is currently of great interest to allergists/immunologists in the United States. For over a decade they have been reading reports of the safety and efficacy of this approach to allergen immunotherapy; for several years they have been presented with at their meetings and in their journals the results of studies of SLIT conducted in the United States, and now there is the expectation of impending approval of some SLIT preparations by the Food and Drug Administration (FDA).

However, SLIT is not altogether new to the United States. In 1971, Lawrence Dickey reported in *JAMA* that the administration of antigens sublingually dated at least back to its use by French Hansel in 1945 [1]. Dr Dickey, himself, had been taught the approach in 1963 and, over the next 7 1/2 years, had personally treated 1356 patients with sublingual antigen therapy. He further

reported that, in those same 7 1/2 years, over 1000 physicians had received training in SLIT at postgraduate allergy courses and workshops at the annual meetings of the American Society of Ophthalmologic and Otolaryngologic Allergy. The treatment that was administered consisted of one or three drops daily. The extract concentration was determined by intracutaneous 1:5 serial dilution titration to endpoint. This approach to determining optimal immunotherapy dosage, which was first described by Rinkle, was later studied in subcutaneous immunotherapy and found to produce

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KEY POINTS

- SLIT is clinically effective when initiated 4 months prior to the ensuing pollen season.
- Effective and well tolerated doses have been established with both tablet and liquid preparation of short ragweed and for two different tablets of grass.
- Multiyear studies and studies following discontinuation of treatment have been and are being conducted in Europe, but none has been reported in the United States.
- The appropriate management of the patient with multiple clinically important sensitivities has not been addressed.

results indistinguishable from the placebo [2,3]. None of these approaches to SLIT was subjected to randomized, controlled study.

Perhaps in part because of the practice of SLIT in the United States in an unproven and possibly ineffective manner, American allergist/immunologists have been slow to incorporate this form of immunotherapy in their practices [4,5]. Other major barriers have been the lack of FDA-approved extracts for sublingual administration, unknown effective doses, and cost [4,5]. Now, with FDA approval pending and with third-party reimbursement likely to follow, it seems an appropriate time to review the more recent, adequately controlled studies that have been conducted in the United States.

RANDOMIZED, CONTROLLED STUDIES IN THE UNITED STATES

Within the last few years studies of SLIT have been conducted in the United States employing allergen tablets that were developed in Europe and with liquid allergen extracts already approved for use in subcutaneous immunotherapy in the United States. All of these studies have been limited to those allergens that have been standardized by the FDA – grass, short ragweed, cat hair and dander, and house dust mites.

A preliminary safety and dose determining study [6] was conducted in 2005 with four FDA-approved standardized liquid extracts. Ninety-one adults with allergic rhinitis with or without intermittent asthma underwent a 1-day up dosing with six incremental doses of timothy or short ragweed pollen extracts or four incremental doses of cat or house dust mite extracts. The maximum doses and the percentage achieving the maximum dose were: timothy grass 14 000 BAU (33%), short

ragweed 60.2 Amb a 1-Units (40%), house dust mite 1400 AU (80%), and cat hair and dander 1400 BAU (69%). During up dosing, 45% reported one or more moderate adverse effects. No severe reactions were reported. The individuals then continued the highest tolerated dose daily for 8 weeks. During that period 24 756 adverse effects were reported 94.6% mild, 5.2% moderate, and 0.1% severe. 9.1% of adverse effects were systemic (affecting lungs or skin). None was life-threatening. No outcomes were recorded.

Studies with grass tablets

Five studies [7–10,11^{*}] have been conducted in the United States with grass pollen extract tablets (Table 1). The first study with the timothy tablets did not demonstrate statistically significant improvement with the active treatment compared with placebo. The possible reasons for this failure have been recently discussed [7]. The results from the other four studies are summarized in Table 1. All are single-season studies, conducted with optimal doses previously identified in European studies, and initiated with daily treatment 4 months prior to and through the grass pollen season. The improvement in combined symptom/medication scores, compared with placebo, ranged from 20 to 28.2% for the entire grass pollen season.

Studies with grass liquid

No efficacy studies have been conducted with liquid grass pollen extracts.

Studies with short ragweed tablets

In addition to two 28-day safety studies [12], two 52-week safety and efficacy studies have been conducted, one in North America, Russia, Hungary, and the Ukraine [13^{*}] the other in North America alone (Table 2) [14]. The primary outcome in these two trials was total combined scores (TCS) during the peak ragweed season. Unlike the grass studies, these were dose-finding studies. The results with the lowest dose containing 1.5 Amb a 1-Units were not significantly different from placebo. Doses containing 6 Amb a 1-Units reduced TCS by 19–21%, whereas those containing 12 Amb a 1-Unit reduced TCS by 24–26%.

Studies with short ragweed liquid

Two studies have been performed, one a dose-ranging study with individuals receiving either placebo or short ragweed extract containing 4.8 or

Table 1. Studies in the United States with grass pollen extract tablets

Author (refs)	Number	Preparation	Duration	Primary outcome	Secondary outcomes	TRAE	Systemic TRAE	TR serious reactions
Nelson <i>et al.</i> [8]	439 18–65 years	Timothy 15 µg Phl p 5, 2800 BAU daily	4-month preseasonal and coseasonal	TCS entire GPS 20%, $P=0.005$	RQLQ 17%; IgG ₄ and IgE blocking factor ↑	Active 72.8% placebo 27.6%	1 grade 1 anaphylactic reaction	None
Blaiss <i>et al.</i> [9]	345 5–17 years	Same	Same	Same 26% $P=0.001$	RQLQ 18% IgG ₄ and IgE blocking factor ↑	Active 70% placebo 25%	Urticaria 3 Asthma 1	None
Maloney <i>et al.</i> [10]	1501 5–65 years	Same	Same	Same 23% $P<0.001$	Peak RQLQ 18% $P=0.042$	Not reported	2 moderate	None
Cox <i>et al.</i> [11]	453 18–65 years	5-grass 25 µg group 5 daily	Same	Same 28.2% $P=0.0003$	Peak RQLQ 21% $P=0.0042$	Active 54.9% placebo 22.5%	No anaphylaxis	None

BAU, bioequivalent allergy units; GPS, grass pollen season; RQLQ, rhinitis quality of life questionnaire; TCS, total combined score; TR, treatment related; TRAE, treatment-related adverse effects.

Table 2. Studies performed in the United States with short ragweed pollen allergen tablets

Author (refs)	Number	Preparation	Duration	Primary outcome	Secondary outcomes	TRAE	Systemic TRAE	TR serious reactions
Creticos <i>et al.</i> [13] (North America, Ukraine, and Hungary)	784 18–50 years	Short ragweed tablets containing 1.5, 6, or 12 Amb a 1-Units or placebo	16 weeks preseasonal, total 52 weeks	TCS during peak of ragweed season. 9% NS, 19% $P=0.01$, and 24% $P=0.002$ ↓ with the three doses	Those with local application site reactions 23% ↓ Those without local application site reactions 33% ↓	Placebo 23% 1.5 U 40% 6 U 52% 12 U 54%	None	None
Nolte <i>et al.</i> [14] (North America)	565 adults	Short ragweed tablets containing 6 or 12 Amb a 1-Units or placebo	16 weeks preseasonal, total 52 weeks	TCS during peak ragweed pollen season. 21% ↓ with 6 U, 26% ↓ with 12 U	During entire pollen season: 6 U 21% ↓ 12 U 27% ↓	Placebo 8% 6 U 29% 12 U 33%	None	None

TCS, total combined score; TR, treatment related; TRAE, treatment-related adverse effects.

Table 3. Studies performed in the United States with short ragweed pollen allergen liquid

Author (refs)	Number	Preparation	Duration	Primary outcome	Secondary outcomes	TRAE	Systemic TRAE	TR serious reactions	
Skoner [15]	115	18–50 years	Short ragweed liquid extract containing 4.8 µg Amb a 1 or 48 µg Amb a 1	1-day three to four step up dosing. 8–10 weeks preseasonal and coseasonal	Daily symptom score. 15% N.S.	Medication score P=0.048. ANCOV P=0.05 high dose	Oral-mucosal side-effects placebo 0%, medium dose 13%, and high dose 11%	One each: eye swelling, skin rash, and GI symptoms	None
Cretricos [16]	429	18–55 years	Short ragweed pollen liquid extract containing 50 Amb a 1-Units daily (94%) or 18 Amb a 1-Units (6%)	1-day three-step up dosing. 8–16 weeks preseasonal and coseasonal	Combined symptom-medication score (change from baseline) during peak 3 weeks. 42% ↓	TCS (change from baseline) during peak 3 weeks. 42% ↓	Not reported	None	None

ANCOV, analysis of covariance; GI, gastrointestinal; TR, treatment related; TRAE, treatment-related adverse effects.

48 µg of Amb a 1 (Table 3) [15], the other targeting at a dose containing 50 µg of Amb a 1 but with 6% receiving only 18 µg of Amb a 1 [16]. The percentage improvement is reported only for the second and larger study. The TCS was reduced 42% for the entire ragweed season and 43% for the peak. However, the results were reported as the comparison of change from baseline rather than comparison of TCSs. If the TCSs for placebo and ragweed treated groups are compared, the improvement is only 20%.

Studies with perennial allergens

Two small studies have been conducted with perennial allergens. Although lacking in statistical power, both showed some evidence of efficacy with high-dose SLIT.

Cat

A double-blind, placebo-controlled study [17] of sublingual cat immunotherapy was conducted in 41 cat-sensitive adults with rhinitis, with or without asthma in the early 1990s. Individuals in the active treatment group receive, after 15 days of up dosing, 90 days of treatment with 20 drops daily of a 10 000 AU/ml standardized cat hair and dander extract. Primary outcomes were rhinitis/conjunctivitis/asthma symptoms and changes in nasal peak inspiratory flow recorded every 15 min during 90-min exposure in an apartment with four cats. As compared with baseline, symptom scores decreased 58% ($P<0.001$) in the active and 47% ($P<0.01$) in the placebo, and nasal blockage index decreased 86% ($P<0.001$) in the active and 21% (N.S.) in the placebo. The changes did not differ significantly between groups.

House dust mite

Thirty-one individuals with allergic rhinitis, with or without asthma, sensitive to *Dermatophagoides farinae* were randomized to high-dose SLIT (4200 AU or approximately 70 µg of Der f 1/day), low-dose SLIT (60 AU or approximately 1 µg of Der f 1/day), or placebo [18]. Only 21 patients completed 12–18 months of participation. At 12 months, there were no differences among groups in symptoms or medication use. Bronchial allergen challenges after 12–18 months of treatment showed a significant increase in the bronchial threshold in the high-dose group compared with those receiving placebo ($P=0.04$).

Studies with multiple-allergen extracts

Virtually all of the published studies of SLIT have employed single allergen extracts. Such

monotherapy is commonly practiced in Europe, but is very uncommon in the United States [19]. To date, only three studies have been published that employed more than one extract. This includes an open-label study of coadministration of birch and timothy grass extracts conducted in Italy, that showed effects comparable to monotherapy with the same extract [20], and two double-blind, placebo-controlled studies conducted in the United States [21,22].

Of 30 children and adults who were allergic to both timothy grass and house dust mites, 20 received SLIT, whereas 10 received placebo-SLIT for 12 months [21]. The maintenance dose was 2800 BAU of timothy extract and 2800 AU of house dust mite extract administered daily, at the same time, from separate bottles. During the ensuing grass pollen season (4–6 months following completion of SLIT) symptoms were reduced in the active group by 38% compared with no change in the placebo group ($P=0.001$). The improvement in symptoms during the grass pollen season was accompanied by a significant improvement in the active group on nasal allergen challenge. Comparable assessments were not made of the clinical response to the house dust mite immunotherapy. However, the results support the clinical effectiveness of SLIT administering two allergens simultaneously.

A study [22] was conducted to examine the customary prescribing practice of immunotherapy in the United States. Fifty-four grass allergic patients received either timothy grass alone, the same dose of timothy grass combined with nine unrelated pollen extracts, or placebo sublingually daily for 10 months [19]. The principal outcomes were titrated prick skin tests, titrated nasal allergen challenges, and timothy-specific IgG₄ antibodies. Although there were favorable trends in the multiple-allergen group, significant improvement with both titrated prick skin tests and titrated nasal allergen challenge was observed only in those receiving the timothy monotherapy. The results suggest caution in extrapolating the results from SLIT monotherapy to SLIT with multiple-allergen mixes.

CONCLUSION

Carefully designed, large, randomized, placebo-controlled studies of SLIT have now been conducted in the United States with pollen allergens of grass(s) and short ragweed. These have demonstrated significant efficacy in the first year of treatment and an acceptable safety profile for home administration after the first dose. It is anticipated that these

studies will provide to the FDA sufficient evidence of safety and efficacy to result in approval within the near future. The principal remaining unanswered question is how to deal with the patient with more than two clinically relevant sensitivities.

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Conflicts of interest

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